

**Coexistence of Two Competitors On
One Resource and One Inhibitor:
A Chemostat Model Based on Bacteria and Antibiotics**

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We present a continuous time model of the dynamics of two species competing for a single limiting resource in the presence of a substance that inhibits the growth of one of the species. Resource and inhibitor are both derived from external sources. These inputs, and all other model parameters, are assumed to be constant in space and time. There exist conditions that permit the stable coexistence of the competitors, provided that (i) the sensitive species is more efficient in exploiting the limiting resource, and (ii) the resistant species removes the inhibitor from the environment. There exists a subset of these conditions wherein the sensitive species can become established if and only if the resistant species is already established. If the resistant species does not remove the inhibitor from the environment, then coexistence of sensitive and resistant species is structurally unstable. If the resistant species produces the inhibitor, then coexistence is dynamically unstable. We review several studies of bacterial competition in the presence of antibiotics that support these conclusions.

Introduction

According to an outmoded version of the competitive exclusion principle, the number of species that can coexist indefinitely cannot exceed the number of distinct resources. Fredrickson & Stephanopolous (1981) and Abrams (1983) provide recent reviews of demonstrable exceptions to this principle. For example, temporal variability in the supply of a single resource may allow two species to coexist, although not at constant population densities (Stewart & Levin, 1973; Levins, 1979; Armstrong & McGehee, 1980; Tilman, 1982). Also, if some species are limited by factors other than competition, then the number of species that can stably coexist may exceed the number of resources. The most familiar situation is predator or parasite mediated coexistence of two prey or host species competing for a single resource, which can occur if the inferior competitor is resistant to exploitation (Levin, 1970; Levin *et al.*, 1977). Moreover, stable coexistence of two species on a single resource may arise via interference competition, provided that each species inhibits its own

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population growth more strongly than that of the other species (DeFreitas & Fredrickson, 1978; Schoener, 1978; Vance, 1985). Types of interference mechanisms include agonistic behaviors and the production of inhibitory substances.

Little attention has been paid to inhibitory substances like pesticides that are derived from external sources, and are not produced *in situ* by the competing species. In this paper, we examine the conditions under which an externally derived inhibitor can promote the stable coexistence of two species competing for a single resource in a homogeneous environment. We also review observations from experiments with bacteria and antibiotics that support the conclusions drawn from our model.

The Model

Our model assumes an open habitat, such as a chemostat for the continuous culture of microorganisms (Kubitschek, 1970). Two species compete for a single limiting resource in the presence of an inhibitor to which one species is sensitive and the other resistant. Let C and X be the concentrations of the resource and the inhibitor, respectively. Let S and R be the respective densities of the sensitive and resistant species.

Resource and inhibitor enter the habitat at concentrations C_0 and X_0 , respectively, via a constant flow rate ω . Sensitive and resistant species are washed out of the habitat at this same rate, as are unused resource and inhibitor. Both species have per capita rates of resource uptake and population growth that are hyperbolic functions of resource concentration. When resource is superabundant, growth occurs at a maximum rate ψ . At resource concentration K , growth occurs at half this maximum. Each production of a new individual requires ϵ units of resource conversion. Subscripts S and R denote these parameters for sensitive and resistant species, respectively. The rates of resource uptake and growth of the sensitive species are also negative exponential functions of inhibitor concentration. The degree of sensitivity is determined by the coefficient λ . Where specifically indicated, the resistant species removes the inhibitor from the environment at a per capita rate that is a hyperbolic function of inhibitor concentration. The maximum rate at which this detoxification occurs is δ , and L is the inhibitor concentration at which the rate is half maximum.

The following equations summarize the dynamics of resource, sensitive species, resistant species, and inhibitor, respectively

$$\dot{C} = (C_0 - C)\omega - \epsilon_S S \psi_S e^{-\lambda X} \frac{C}{K_S + C} - \epsilon_R R \psi_R \frac{C}{K_R + C} \quad (1)$$

$$\dot{S} = S \psi_S e^{-\lambda X} \frac{C}{K_S + C} - \omega S \quad (2)$$

$$\dot{R} = R \psi_R \frac{C}{K_R + C} - \omega R \quad (3)$$

$$\dot{X} = (X_0 - X)\omega - R \delta \frac{X}{L + X} \quad (4)$$

where the dot notation indicates differentiation with respect to time.

Although we have chosen to specify the functions describing resource utilization, population growth, growth inhibition, and inhibitor detoxification, it will be shown that the general theoretical conclusions that follow are not dependent on the specific form of these equations.

COEXISTENCE AND STABILITY WITHOUT DETOXIFICATION

Let us first consider the conditions for the equilibrium coexistence of sensitive and resistant species when there is no detoxification of the inhibitor. Inspection of eqns (2) & (3) reveals that both can be set to zero if and only if the per capita growth rates of the sensitive and resistant species are identical, and equal to the rate of loss due to washout. One obtains the equilibrium concentration of resource by setting eqn (3) equal to zero

$$\hat{C} = \frac{\omega K_R}{\psi_R - \omega} \quad (5)$$

Note that this same equilibrium concentration of resource would result even in the absence of a sensitive population. One obtains the equilibrium concentration of inhibitor by setting eqn (2) equal to zero

$$\hat{X} = -\frac{1}{\lambda} \log_e \left(\frac{\omega \hat{C} + \omega K_S}{\psi_S \hat{C}} \right) \quad (6a)$$

However, if there is no detoxification of the inhibitor by the resistant population, then from eqn (4) the equilibrium concentration of inhibitor must also be exactly equal to its influx concentration

$$\hat{X} = X_0 \quad (6b)$$

It is also possible to obtain a measure of the combined equilibrium densities of the sensitive and resistant populations by setting eqn (1) to zero

$$\epsilon_S \hat{S} + \epsilon_R \hat{R} = C_0 - \hat{C} \quad (7)$$

where each density has been weighted by its resource conversion equivalent. It is not possible, however, to specify the equilibrium densities for each species.

If the influx concentration of inhibitor exceeds the critical concentration given by eqn (6a), then the sensitive species is excluded by the resistant species. That is, the resistant population drives the resource concentration below that level which permits the net replacement of the sensitive population. On the other hand, if the influx concentration of inhibitor is less than this critical concentration, then the sensitive species excludes the resistant species by driving the resource concentration too low. An alternative means for obtaining the critical influx concentration of inhibitor that permits coexistence would therefore be to equalize the equilibrium resource concentrations that would obtain for each species in the absence of the other.

The preceding argument is identical to that of Hansen & Hubell (1980), and parallels the general result of mechanistic chemostat models wherein the winning competitor is the one with the lowest "break-even" concentration of limiting resource

(Stewart & Levin, 1973; Hsu *et al.*, 1977; Tilman, 1982; Waltman, 1983). This argument also implies that the sensitive species must be competitively superior to the resistant species in the absence of inhibitor, if the species are to coexist in the presence of the inhibitor. That is, removal of the inhibitor reduces the resource concentration required for net replacement of the sensitive species, but not of the resistant species.

The influx concentrations of resource and inhibitor that permit establishment and coexistence are shown in Fig. 1(a) for a particular set of parameters. Neither species

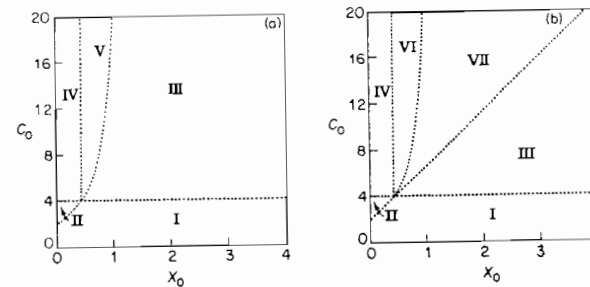


FIG. 1. Outcomes of competition between sensitive (*S*) and resistant (*R*) species. C_0 and X_0 are influx concentrations of resource and inhibitor, respectively. I—neither *S* nor *R* can establish. II—only *S* can establish. III—only *R* can establish. IV—either *S* or *R* can establish alone; *S* excludes *R*. V—either *S* or *R* can establish alone; *R* excludes *S*. VI—either *S* or *R* can establish; *S* and *R* can coexist. VII—only *R* can establish alone; *S* and *R* can coexist. (a) Without detoxification of the inhibitor by the resistant species ($\delta = 0$). (b) With detoxification of the inhibitor by the resistant species ($\delta = 1 \times 10^{-6}$). (a) & (b) $\omega = 0.2$; $\psi_S = \psi_R = 0.7$; $\epsilon_S = \epsilon_R = 1 \times 10^{-6}$; $K_S = 5$; $K_R = 10$; $\lambda = 1$; $L = 10$.

can become established in the region designated I, where the resource concentration is too low and/or the inhibitor concentration too high. Only the sensitive species can establish in region II, while only the resistant species in region III. Regions IV and V correspond to conditions where either species can become established when alone, but where sensitive and resistant species, respectively, prevail in competition with one another. Coexistence is possible only along the boundary between regions IV and V. Any deviation in the influx concentration of inhibitor, however slight, from the critical value given by eqn (6a) destroys this equilibrium. Therefore, without detoxification, the equilibrium specifying coexistence of sensitive and resistant species is structurally unstable.

COEXISTENCE AND STABILITY WITH DETOXIFICATION

Let us now assume that the resistant species detoxifies the inhibitor, and consider the conditions for stable coexistence of sensitive and resistant species on a single resource. As was the case without detoxification, the per capita growth rates of sensitive and resistant populations must be identical, and equal to the flow rate, at

equilibrium. Once again, this implies that the equilibrium concentration of inhibitor must be equal to the critical value given by eqn (6a). However, the influx concentration of inhibitor need not be equal to that critical value. That is, detoxification by the resistant species reduces the concentration of inhibitor below its influx concentration, so eqn (6b) no longer holds. The sensitive species thus experiences a reduced concentration of inhibitor, as well as of resource, in the presence of the resistant species.

We have already obtained the equilibrium concentration of resource, such that the rates of growth and washout in the resistant population are exactly equal (eqn (5)). We have also already obtained the equilibrium concentration of inhibitor, which yields an identical per capita rate of growth for the sensitive population (eqn. (6a)). Because the detoxification parameter is now greater than zero, one can set eqn (4) to zero, and thereby obtain the equilibrium density of the resistant competitor

$$\hat{R} = \omega(X_0 - \hat{X}) \frac{\hat{X} + L}{\delta \hat{X}}. \quad (8)$$

From eqn (1), one can then solve the equilibrium density of the sensitive competitor consistent with the other equilibrium values

$$\hat{S} = \frac{C_0 - \hat{C} - \epsilon_R \hat{R}}{\epsilon_S} \quad (9)$$

Note that the equilibrium densities of sensitive and resistant populations still satisfy the relationship in eqn (7). The density of the resistant species can thus be interpreted as that fraction of the combined density that provides just the rate of detoxification necessary to reduce the influx of inhibitor to its critical equilibrium concentration.

Having derived the equilibrium densities for the sensitive and resistant populations, we can now examine the conditions permitting their coexistence. Note first that the presence of a sensitive population in no way benefits the resistant population, which simply experiences a reduced availability of resource. In contrast, the sensitive species experiences a reduced concentration of inhibitor, as well as of resource, in the presence of the resistant population. This implies that the conditions for coexistence with detoxification must be a subset of the conditions where the resistant species prevails without detoxification.

Recall that the equilibrium concentration of resource from eqn (5) obtains whether or not the sensitive population is present. The equilibrium density of the resistant population when alone thus equals the total resource equivalent density in eqn (7). For the sensitive species to invade a resistant population at equilibrium, the resistant population must reduce the influx inhibitor concentration below the critical equilibrium value given by eqn (6a). This condition is met when the influx concentrations of resource and inhibitor satisfy the following inequality

$$\frac{C_0 - \hat{C}}{\epsilon_R} \delta \frac{\hat{X}}{\hat{X} + L} > (X_0 - \hat{X}) \omega. \quad (10)$$

In Fig. 1(b), we have graphed the possible equilibrium outcomes as a function of the influx concentrations of resource and inhibitor, for the same parameters as

in Fig. 1(a), except that the resistant population now detoxifies the inhibitor. Region VI includes those conditions where either species could establish alone, and where there exists an equilibrium specifying coexistence of the two species. It is a subset of region V in Fig. 1(a), wherein the resistant species would competitively exclude the sensitive species without detoxification. (For the parameter values used to generate Fig. 1, region VI in frame b completely overlaps region V in frame a. With other parameter values, region VI may overlap only a portion of region V.) Region VII also includes conditions where sensitive and resistant populations can coexist, but where the sensitive species cannot become established unless the resistant species is already present; it is a subset of region III in Fig. 1(a). Region VII thus corresponds to obligatory succession, wherein one species requires another to favorably modify the environment and thus facilitate its invasion (Horn, 1981).

It should be noted that the equilibrium concentrations of resource and inhibitor are independent of their concentrations as they enter the habitat, whenever the resistant and sensitive species can coexist (regions VI and VII). These equilibrium concentrations appear graphically as the point intersection of all the boundaries between regions.

Let us now examine the stability properties of the model in the neighbourhood of the equilibrium specifying coexistence of the sensitive and resistant species. We present each of the elements of the community matrix associated with eqns (1)-(4) in the appendix. We indicate the signs of these elements in Fig. 2, using the notation

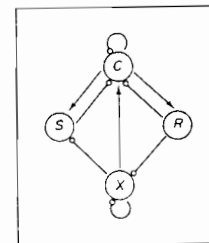


FIG. 2. Loop diagram of the community with sensitive (*S*) and resistant (*R*) species coexisting on one resource (*C*) and one inhibitor (*X*). Lines with arrows indicate positive effects; lines with circles indicate negative effects; no lines indicate zero effects. Signs of effects are determined from the community matrix that is given in the Appendix. The negative effect of *R* on *X* becomes positive if the resistant species produces the inhibitor.

of Levins (1975). Any equilibrium of interest is stable if and only if all of the eigenvalues of the community matrix have negative real parts when evaluated at that equilibrium (May, 1974; Levins, 1975). The equation for the eigenvalues is a polynomial, and the Routh-Hurwitz theorem specifies the relationships between the coefficients of the polynomial that ensure that all eigenvalues have negative real parts. Without belaboring the mathematical complexities associated with determining whether or not these relationships are satisfied, two distinct criteria must be met.

The first criterion for stability requires that net feedbacks at all levels must be negative. In the Appendix, we show that net feedbacks of length 1 to 3 are negative, whether or not the resistant species detoxifies the inhibitor. The critical condition for stability is found at level 4. Without detoxification, the effect of R on X in Fig. 2 becomes zero; no loops of length 4 are possible, nor are there any disjunct loops of combined length 4. Hence, the net feedback at level 4 is zero without detoxification, violating the criterion that net feedbacks at all levels must be negative for neighbourhood stability. The zero feedback does, however, indicate a zero real part for one of the eigenvalues of the community matrix, and this in turn implies an equilibrium with structural instability. In fact, we computed a critical influx concentration of inhibitor that was necessary to yield an exact equivalence in the growth rates of the sensitive and resistant species (eqns 6(a) and 6(b)). Without detoxification, any deviation in this parameter, however slight, would necessarily provide a growth advantage to one species or the other, and thus destroy the equilibrium.

If there is detoxification of the inhibitor by the resistant species, we have a single loop of length 4 ($CRXS$), and the product of the signs along this loop is negative. The stabilizing effect of detoxification can be seen intuitively by imagining a perturbation of the following sort. If the density of the sensitive competitor is reduced then its use of resource declines, thereby leading to an increase in resource concentration. This in turn stimulates the growth of the resistant population, resulting in a higher rate of detoxification of the inhibitor. As a consequence of the reduced concentration of inhibitor, the sensitive population experiences an increased growth rate, thereby opposing the effect of the original perturbation.

Detoxification thus produces a negative feedback that is necessary for stable coexistence of the sensitive and resistant species. This conclusion is robust, and depends only on the signs of the elements of the community matrix. It is therefore not dependent on the exact form of the functions used in eqns (1)–(4) to describe the processes of resource utilization, population growth, growth inhibition, and inhibitor detoxification.

The second criterion for stability specifies that the magnitudes of the feedbacks must be such that longer feedbacks do not overwhelm shorter feedbacks. Its violation is analogous to the introduction of a time delay into one or more of the differential equations. In the Appendix, we show that this criterion may be violated by reducing the responsiveness of the growth rate of the sensitive species to the resource concentration; or by reducing the responsiveness of the detoxification rate of the resistant species to the inhibitor concentration. These changes, in effect, remove constraints that generally limit the rates of biological processes when substrates are at low concentration, and should be considered unlikely. In summary, detoxification is necessary for (but does not ensure) the stable coexistence of sensitive and resistant species on one resource and one inhibitor (both externally derived) in a homogeneous environment.

Discussion

As noted by Williamson (1972), commensalistic interactions between species have received insufficient consideration in ecological theory. One type of commensalism

is detoxification of an inhibitor, which we have shown can stabilize an otherwise unstable competitive interaction. Detoxification of externally derived inhibitors, including pollutants, may be very important in nature, especially in microbial communities (Bull & Slater, 1982). Resistance by bacteria to antibiotics and heavy metals, for example, frequently results from the acquisition of an extrachromosomal element, or plasmid, that encodes an enzyme which converts the inhibitor into a less toxic form (Foster, 1983).

The antibiotic chloramphenicol is detoxified by its enzymatic acetylation. This reduces the intracellular concentration of chloramphenicol, and thereby enables the survival of bacteria that produce the enzyme. It also results in a significant decline in the concentration of the antibiotic in the environment (Lundback & Nordstrom, 1974). Hattings (1986) has shown that carriage by *Escherichia coli* of a non-self-transmissible plasmid encoding this detoxification activity engenders a pleiotropic reduction in competitive ability; in the absence of chloramphenicol, plasmid-bearing cells decline rapidly in frequency when allowed to compete with plasmid-free cells in chemostat culture. Hattings (1986) further demonstrated that plasmid-free cells could invade a chemostat with an influx of $2.5 \mu\text{g}$ per ml of chloramphenicol only if plasmid-bearing cells were already established. With no antibiotic in the culture medium, plasmid-free cells could invade whether or not plasmid-bearing cells were present. These experimental results confirm the critical features of the model presented in this paper.

Hansen & Hubbell (1980) examined competition between *E. coli* strains sensitive and resistant to another antibiotic, nalidixic acid. In this case, however, resistance was due to a chromosomal mutation that renders the strain insensitive to the effects of nalidixic acid, but does not result in detoxification of the antibiotic. Hansen & Hubbell (1980) demonstrated that the sensitive and resistant strains could coexist only if the influx concentration of nalidixic acid ($0.5 \mu\text{g}$ per ml) was chosen to yield an exact equivalency in the "break-even" concentration of the limiting resource for the two strains. This result illustrates their contention that resource-based competition theory is preferable to classical competition theory. It is also consistent with our contention that coexistence of two competitors on one resource and one externally derived inhibitor is structurally unstable, unless the resistant species removes the inhibitor from the environment.

DETOXIFICATION VERSUS ALLELOPATHY

In our model, we have assumed that the inhibitor is derived from an external source. We now briefly contrast the situation in which the inhibitor is an allelopathic substance, produced by the resistant species. This is one of several cases involving *in situ* production of inhibitors that have been considered theoretically by DeFreitas & Fredrickson (1978). We can readily alter our loop diagram for the detoxification model (Fig. 2) to incorporate this allelopathy. The negative effect of the resistant species on the inhibitor becomes positive, and the feedback along the loop $CRXS$ is also positive. Because there are no other feedbacks at this level, coexistence is necessarily unstable. The destabilizing effect of allelopathy can be seen intuitively

by imagining the following perturbation. A reduction in the density of the sensitive competitor leads to an increase in resource concentration. This stimulates the growth of the resistant population, resulting in an increase in the concentration of the allelopathic substance. As a consequence, the sensitive population experiences a reduced growth rate, thus exacerbating its original decline.

Once again, experimental communities of bacteria provide a confirmation of this theoretical prediction. Several studies have examined competition between two strains of *E. coli*, where one produced a toxin to which it was resistant and its competitor was sensitive (Zamenhof & Zamenhof, 1971; Adams *et al.*, 1979; Chao & Levin, 1981). Each demonstrated that the allelopathic strain could increase only when it was above a certain initial frequency in the community; it declined whenever it was below that frequency, thus indicating an unstable equilibrium.

The inability of the allelopathic strain to increase when rare, though consistent with ecological theory, appears problematic from an evolutionary perspective. How can allelopathy become established if it is selectively disadvantageous when rare? Chao & Levin (1981) suggested a resolution to this paradox by demonstrating that the allelopathic strain had an advantage even when rare if the competitors interacted not in liquid culture, but on the surfaces of agar plates. The explanation for this result is that on surfaces bacteria exist as discrete colonies. Allelopathic colonies kill neighboring sensitive colonies and thus sequester local resources. In contrast, any resource made available by the action of inhibitor in liquid culture is distributed randomly by the laws of mass action, and is thus equally available to sensitive and resistant cells.

In contrast to the allelopathic trait considered by Chao & Levin (1981), there is no difficulty in identifying ecological conditions in which the detoxification trait could increase when rare, even in liquid culture. Of course, the effect of antibiotic detoxification, like that of allelopathy, could be locally amplified in a structured habitat, perhaps limiting opportunities for coexistence of sensitive organisms. However, detoxification of the *extracellular* environment is probably not an adaptation *per se*, but rather a consequence of the on-going detoxification of the *intracellular* environment.

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APPENDIX

The following partial differential equations define the elements of the community matrix for the model presented in eqns (1)-(4).

$$\partial \dot{C} / \partial C = -\omega [1 + \epsilon_S \hat{S} K_S / (\hat{C}^2 + \hat{C} K_S) + \epsilon_R \hat{R} K_R / (\hat{C}^2 + \hat{C} K_R)]$$

$$\partial \dot{C} / \partial S = -\omega \epsilon_S$$

$$\partial \dot{C} / \partial R = -\omega \epsilon_R$$

$$\partial \dot{C} / \partial X = \omega \epsilon_S \lambda \hat{S}$$

$$\partial \dot{S} / \partial C = \omega \hat{S} K_S / (\hat{C}^2 + \hat{C} K_S)$$

$$\partial \dot{S} / \partial S = 0$$

$$\partial \dot{S} / \partial R = 0$$

$$\partial \dot{S} / \partial X = -\omega \lambda \hat{S}$$

$$\partial \dot{R} / \partial C = \omega \hat{R} K_R / (\hat{C}^2 + \hat{C} K_R)$$

$$\partial \dot{R} / \partial S = 0$$

$$\partial \dot{R} / \partial R = 0$$

$$\partial \dot{R} / \partial X = 0$$

$$\partial \dot{X} / \partial C = 0$$

$$\partial \dot{X} / \partial S = 0$$

$$\partial \dot{X} / \partial R = -\delta \hat{X} / (\hat{X} + L)$$

$$\partial \dot{X} / \partial X = -\omega - \delta \hat{R} L / (\hat{X} + L)^2$$

Although non-zero terms appear in $\partial\dot{S}/\partial S$ and $\partial\dot{R}/\partial R$, they cancel by virtue of the derivations for \dot{C} and \dot{X} (eqns. (5) and (6a)). The signs of these elements are robust, and not dependent on the exact form of the functions used to describe the processes of resource utilization, population growth, growth inhibition, and inhibitor detoxification. These signs are shown schematically in Fig. 2.

Net feedbacks at each level are computed according to Levins (1975). f_i is the sum of the products along all loops of length i , plus the sum of the products along all disjunct loops whose combined length is i . The sign of a product of disjunct loops is adjusted so as to be negative if the products along all of the constituent loops are negative. Negative net feedbacks at all levels are necessary (but not sufficient) for stability.

$$f_1 = (\partial\dot{C}/\partial C) + (\partial\dot{X}/\partial X)$$

$$f_2 = (\partial\dot{C}/\partial S)(\partial\dot{S}/\partial C) + (\partial\dot{C}/\partial R)(\partial\dot{R}/\partial C) - (\partial\dot{C}/\partial C)(\partial\dot{X}/\partial X)$$

$$f_3 = (\partial\dot{C}/\partial X)(\partial\dot{R}/\partial C)(\partial\dot{X}/\partial R) - (\partial\dot{X}/\partial X)(\partial\dot{C}/\partial S)(\partial\dot{S}/\partial C)$$

$$- (\partial\dot{X}/\partial X)(\partial\dot{C}/\partial R)(\partial\dot{R}/\partial C)$$

$$f_4 = (\partial\dot{C}/\partial S)(\partial\dot{R}/\partial C)(\partial\dot{X}/\partial R)(\partial\dot{S}/\partial X).$$

Net feedbacks at levels 1 to 3 are negative, whether or not the resistant species detoxifies the inhibitor. Feedback at level 4 is also negative if the resistant species detoxifies the inhibitor, but is zero without detoxification.

Even if net feedbacks at all levels are negative, an equilibrium may be unstable if longer feedbacks overwhelm shorter feedbacks. The Routh-Hurwitz theorem specifies the relationships between net feedbacks at different levels that are necessary for stability (Levins, 1975). When there are 4 levels of feedback, the following inequality must hold (May, 1974, p. 196):

$$a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$$

where each $a_i = -f_i$. Conditions that violate this inequality can be found by decreasing the magnitudes of elements contributing to f_1 and f_2 (but not f_3 and f_4) or by increasing the magnitudes of those elements contributing to f_3 and f_4 (but not f_1 and f_2). This can be accomplished in two different ways. First, lowering K_S decreases the importance of resource-mediated effects, which dominate the shorter feedbacks. Setting $K_S = 0$, $C_0 = 20$, $X_0 = 2.5$, and all other parameters as in Fig. 1(b), violates the Routh-Hurwitz criterion, but the non-trivial equilibrium persists. Second, lowering L while raising λ increases the importance of inhibitor-mediated effects, which dominate longer feedbacks. With $L = 0$, $\lambda = 10$, $C_0 = 20$, $X_0 = 2.5$, and all other parameters as in Fig. 1(b), the Routh-Hurwitz criterion is also violated, although the non-trivial equilibrium is again preserved.